The pharmaceutical composition according to claim 5, wherein the oligonucleotide is from 20 to about 100 nucleotides in length and comprises a sequence selected from the group consisting of SEQ ID NOs:1-30.

20. The method according to Claim 8 wherein said mammal is a human.

21. The method according to Claim 13 wherein said mammal is a human.

22. The method according to Claim 16 wherein said mammal is a human.--

REMARKS

Upon entry of this Amendment, claims 1-22 will be pending. The Examiner's bases for rejecting claims 1-16 are addressed below. The foregoing amendments are made without any intention to abandon the subject matter of the claims as filed, but with the intention that claims of the same, lessor, or greater scope may be pursued in the present application or in a continuation, continuation-in-part, or divisional application. The present amendment does not add new matter.

Support for the amendments can be found throughout the present Specification. In particular, support for the term "or analog thereof" to claims 1-6, 10 and 14, can be found, for example, at page 12, line 5 to page 14, line 24. Support for antisense oligonucleotides from about 7 to about 100 nucleotides in length can be found, for example, at page 15, line 22.

Support for antisense oligonucleotides comprising a sequence complementary to the transcribed region of a neuropilin gene can be found throughout the present Specification, including the sequences disclosed in Table 1 (*see* pages 16 to 17). The neuropilin antisense oligonucleotides of the present invention can be designed using neuropilin cDNA, which corresponds to the transcribed regions of neuropilin genes. Support for an antisense oligonucleotide that "specifically binds to a nucleic acid comprising a sequence corresponding to said transcribed region," can be found, for example, at page 17, lines 10-17, which contains a description of how antisense oligonucleotides of the present invention are selected. In particular, the oligonucleotides are selected by their high potential to bind neuropilin mRNA sequences and by a reduced "false priming" with frequently occurring or repetitive sequences. Further support can be found at page 20, line 15, to page 21, line 9.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 1-5, 8, 13, and 16 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the Applicants regard as the invention.

The Examiner has rejected Claims 1-5, 8, 13 and 16 as being indefinite for the language "about 20... nucleotides" since the size of SEQ ID NOs:1-30 is 20 bases. Applicants have amended Claims 1-5, 8, 13, and 16 to more clearly define the claimed subject matter. Applicants have amended Claims 1-5 such that they no longer refer to SEQ ID NOs:1-30 and, therefore, the claimed oligonucleotides can be smaller than 20 nucleotides in length. Applicants have amended Claims 8, 13 and 16 such that they are directed toward antisense oligonucleotides that are "20 to 100 nucleotides in length."

The Examiner has rejected Claims 1-5, 8, 13 and 16 as being indefinite for the language " as set forth in Table 1." Applicants have amended the claims such that they no longer refer to Table 1.

Applicants believe that the present amendments overcome the Examiner's rejections and that Claims 1-5, 8, 13, and 16 now meet the requirements of §112, second paragraph. Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. §112, first paragraph, enablement.

The Examiner has rejected Claims 5-16 under 35 U.S.C. §112, first paragraph, alleging that the Specification, while being enabling for methods of inhibiting the growth of neuropilin in cells in culture and *via* injection of specific neuropilin antisense sequences to tumor cells in mice, does not reasonably provide enablement for inhibition of any neuropilin gene in any species of whole organism for the therapeutic effects claimed by any antisense having an unspecified length and sequence. September 28, 2000 Office Action, page 3, paragraph 1.

The Examiner has objected to Claim 5 for lack of enablement since it is drawn to a pharmaceutical composition, which implies whole organism application of the claimed composition.

With respect to Claims 6-16, the Examiner alleges that the scope of the invention drawn to any antisense having "about 3 to about 100 nucleotides" is not enabled as broadly claimed because of the unpredictability in the art for the design of functional antisense. September 28, 2000 Office Action, page 4, paragraphs 1 and 2.

Applicants traverse. First, Applicants respectfully disagree with the Examiner's allegation that the antisense oligonucleotides of the present invention have "unspecified length and sequence." As defined by the claims, the antisense oligonucleotides of the present invention are between about 7 and about 100 nucleotides in length and have a sequence complementary to that of the transcribed region of a neuropilin gene. The cDNA sequence of human (SEQ ID NO:33), rat (SEQ ID NO:34) and mouse (SEQ ID NO:35) neuropilin genes are provided in the Specification as filed. Those skilled in the art will appreciate that similar DNA sequences for other neuropilin genes can be readily obtained using techniques well known in the art, for example, by using a basic BLASTN search of GenBank using SEQ ID NO:33, 34 or 35. Alternatively, such sequences may be readily obtained from genomic DNA by methods well known in the art using probes derived from these sequences. The Specification as filed provides clear guidance for selecting antisense oligonucleotides directed to the neuropilin gene sequence (*e.g.* page 21, lines 3-11), using the desired gene sequence together with the parameters provided for such oligonucleotides (*e.g.* page 15, lines 6-9).

Second, the Court in *In re Vaeck* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) states: "It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." Further, "[I]t is not necessary that a patent applicant test all the embodiments of his invention...; what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify the grant of the claims sought." *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.,* 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991).

Furthermore, in *Precision Metal Fabricators Inc. v. Jetstreams Systems Co.,* 6 USPQ2d 1704, 1709 (N.D. Calif. 1988), the Court states: " [t]he enablement requirement does not require that the patent disclose the specific embodiment of the claim; a broad claim can be enabled by the disclosure of a single embodiment".

Applicants submit that the present Specification lists sequences for thirty exemplary antisense oligonucleotides (SEQ ID NO:1 to 30) complementary to the transcribed region of a human neuropilin gene (SEQ ID NO:33) and provides a demonstration that these oligonucleotides effectively decrease neuropilin mRNA expression in human tumor cell-lines (*See* Example 2). In Examples 3 and 4 of the present Specification, Applicants have further demonstrated that antisense

oligonucleotides to neuropilin can effectively decrease the growth of a mammalian tumor and inhibit experimental mammalian metastasis.

Applicants submit, therefore, that the Specification clearly teaches how to select, produce and use the antisense oligonucleotides of the present invention. Applicants have described in the Specification how to select antisense oligonucleotides of the present invention using essential parameters, and how to produce these antisense oligonucleotides (*e.g.* page 22, lines 18-23; page 21, lines 3-11; page 15, lines 6-9). The sequences of the transcribed regions for neuropilin genes other than SEQ ID NO:33, 34 or 35 can readily be obtained by those skilled in the art as described above. The Specification further provides methods to rapidly screen these antisense molecules for their ability to inhibit tumor growth and metastasis *in vitro* (*e.g.* Example 1, page 41, lines 11-24), and *in vivo* (*e.g.* Example 3, page 43, lines 5-13).

The Examiner has also alleged that the antisense oligonucleotides of the present invention are not enabled for *in vivo* applications due to the high level of unpredictability in the art. More specifically, the Examiner cites a number of factors that are believed to be barriers to the use of antisense oligonucleotides *in vivo* and asserts that, in view of these barriers, "trial and error" experimentation beyond what is taught in the Specification would be required to enable the therapeutic use of the these oligonucleotides as claimed in Claims 6-16. September 28, 2000 Office Action, page 4, paragraph 2, to page 6, paragraph 1.

Again, Applicants respectfully traverse. In §2164.01, the MPEP defines the standard for determining whether a specification meets the enablement requirement under 35 U.S.C §112, first paragraph. In particular:

> "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F2.d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

With respect to the amount of experimentation that should be considered undue, the MPEP §2164.01 further states:

> "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni,* 561 F.2d 220, 224, 195 USP 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " *In re Wands,* 858 F2.d 731, 737, 8 USPQ2d 1400,

1404 (Fed. Cir. 1988) (citing *In re Angstadt,* 537 F.2d 489, 502–04, 190 USPQ 214, 217-19 (CCPA 1976)).

Applicants submit that the Specification as filed provides guidance for the selection, optimization, making and testing of the antisense oligonucleotides of the present invention. The present Specification additionally provides guidance for the formulation of pharmaceutical compositions comprising the antisense oligonucleotides of the present invention and methods for their administration to mammals (*e.g.* page 25, line 15 – page 34, line 14). The majority of known therapeutic antisense oligonucleotides are administered without additional carrier or delivery molecules and the injection of "naked" DNA may be employed to effectively administer antisense therapy as evidenced by the Examples and by the prior art (*e.g.* Felgner *et al.,* U.S. Patent No. 5,580, 859; Vitravene™ product monograph; clinical trial protocols for G3139). The Specification further provides guidance for the *in vivo* use of said oligonucleotides (*e.g.* pages 25 to 34 of the Specification).

Applicants submit that the level of skill in the arts of molecular biology and clinical sciences is high, and that "[w]hen an invention, in its different aspects, involves distinct arts, that specification is adequate which enables the adepts of each art, those who have the best chance of being enabled, to carry out the aspect proper to their specialty", *In re Naquin,* 398 F.2d 863, 866, 158 USPQ 317, 319 (CCPA 1968). Applicants submit that, in light of the high level of skill in the pertinent arts, the experimentation that the Examiner alleges to be unacceptable due to its "trial and error" nature would, in fact, be routine. In the development of new pharmaceuticals testing and/or screening is customary.

In *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the Court ruled: "Enablement is not precluded by the necessity for some experimentation such as routine screening." Patent applicants should not be required to limit their invention to specific examples. "[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts" *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976).

Applicants assert that the Specification as filed provides examples of neuropilin antisense oligonucleotides, which, having successfully decreased neuropilin expression *in vitro* (cell culture), have gone on to effectively inhibit growth and metastasis of tumors *in vivo* (mouse model).

Antisense therapy has been accepted as a valid approach in the treatment of many diseases, and as stated in Gerwitz *et al.* (1996) "several ODN reagents have reached clinical trials for a variety of indications including leukemia, cancer and AIDS." Many of these antisense oligonucleotides were initially tested *in vitro* or in mouse models. For example, the antisense molecules G3139, ISIS 5132 and 3521, and LR-3001 were all originally selected on the basis of results obtained in murine models and later progressed to Phase I clinical trials (Ho and Parkinson, (1997) *Semin. Oncol.*, **24**:107-202), and ISIS 2922 entered Phase III clinical trials in 1996 (Branch, 1998) (see also review by Yuen and Sikic, (2000) *Fron. Biosci.* D588-593). Many of these antisense oligonucleotides had already entered clinical trials at the time of filing the present application.

Applicants have provided herewith several publications that further support the utility of mouse models as a predictive tool for clinical effectiveness of anti-cancer treatments and are representative of the state of the art at the time of filing:

1. Schabet and Herrlinger, (1998), *J. Neurooncol.* **38**:199-205, state that pathophysiological, therapeutic and neurotoxic findings in animal models of leptomeningeal metastasis are well transferable to the clinical situation. Treatments that show high efficacy and low neurotoxicity in the model have good prospects to be useful for patients.

2. Boven *et al.*, (1992), *Cancer Res.* **52**:594-5947, indicate that the human tumour xenograft panel is reflective of the clinical data of chemotherapeutic agents.

3. Giovanella *et al.*, (1983), *Cancer* **52**:1146-1152, disclose that heterotransplants of human tumors in nude mice is a predictive system for testing new anticancer agents and in determining optimal treatment schedules and combinations of known drugs.

4. Fujita *et al.*, (1980), *J. Surg. Oncol.* **15**:211-219, demonstrate that there is a good correlation between experimental chemotherapy using human cancer xenografts in nude mice and clinical response to the same chemotherapy.

Because the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating. *See, Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, first paragraph -- Enablement Chemical/Biotechnical Applications.* "Based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a

rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

The evidence provided by Applicant need not be conclusive but merely convincing to one skilled in the art. *See, Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, first paragraph -- Enablement Chemical/Biotechnical Applications.* Thus, the Applicants, absent some definitive scientific basis to conclude that in vitro models do not correlate with whole animal efficacy in this instance, should be allowed to maintain the scope of their claims, without providing clinical efficacy.

With respect to the factors that the Examiner claims are key to antisense therapy (September 28, 2000 Office Action, page 6, paragraph 1), Applicants submit that these are directed mainly to the mechanisms of action of antisense, for which detailed knowledge need not be demonstrated. "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman v. Quigg,* 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989); see also *Fromson v. Advance Offset Plate, Inc.,* 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). In the Examples of the Specification as filed, Applicants have provided a practical demonstration that the antisense oligonucleotides of the present invention function *in vivo* to repress the growth and metastasis of mammalian tumors. It is not necessary for the Applicants to disclose or predict the exact mode of action of the antisense oligonucleotides.

In this respect, Applicants also note that much of the discussion in Branch (1998) is directed to attempts to distinguish between antisense and non-antisense effects of oligonucleotides, *i.e.* their mechanism of action. Branch does not teach that antisense oligonucleotides are not a valid therapeutical approach, and concedes on page 45 that "both ODNs and bioengineered ribozymes can undeniably hit their target". In order to be enabling the Specification must simply demonstrate that the invention works as claimed and provide sufficient guidance to allow one skilled in the art to make and use the invention as claimed. Applicants submit that the Specification as filed meets with these requirements.

Applicants submit that the Specification contains sufficient description to enable a skilled artisan to make and use the antisense oligonucleotides of the invention as claimed. Applicants

therefore respectfully request that the Examiner reconsider and withdraw this §112, first paragraph rejection.

CONCLUSION

On the basis of the foregoing claim amendments and remarks, Applicants respectfully submit that, upon entry, the pending claims will be in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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